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| 09/808,558 | 03/14/2001 | Michael M. Becker | GP068-05.CN3 | 3920 |

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| EXAMINER | |
|---|---|
| CALAMITA, HEATHER | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

| NOTIFICATION DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/808,558 | BECKER ET AL. | |
| | Examiner | Art Unit | |
| | Heather G. Calamita, Ph.D. | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *519-559* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *519-559* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments, and/or Claims*

1. Amendments of June 27, 2007, have been received and entered in full. New claims 519-559 are pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 523, 524, 543 and 544 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "at least about 44 ribonucleotide." The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that values above and below 4 ribonucleotides are permitted. Further, the extent of variance permitted by "about" is unclear in this context. Since the ribonucleotides referred to are whole numbers, "about 4" cannot mean from 3.4 to 3.6 because nucleotides cannot be split in half. Therefore, it is also unclear if "about 4" simply includes 4 or if it also includes 1-4 as well. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 519-559 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al. (USPN 5,925,517) in view of McGall et al. (USPN 6,156,501).

With regard to claim 519, Tyagi et al. teach a probe molecule for use in determining the presence of a target nucleic acid sequence in a sample, the probe comprising complementary first and second base regions that form a hybrid containing at least one ribonucleotide wherein the probe forms a stable complex with the target nucleic acid sequence but not with a non-targeted nucleic acid under nucleic acid assay conditions such that the target nucleic acid sequence can be detected and wherein the complex comprises a single stranded form of the probe (see Figures 3 and 9. With respect to the "at least one ribonucleotide see claim 20 and col. 8 lines 66-67) and

a solid support for immobilizing the target nucleic acid sequence so that unbound nucleic acid and other components of the sample can be removed (see col. 22 line 21, where the support is magnetic beads and the probe is bound to the support either before or after capturing the target strand)

With regard to claim 520, Tyagi et al. teach a magnetic support (see col. 22 line 21).

With regard to claim 521, Tyagi et al. teach the kit further comprising

a nucleic acid polymerase (see col. 24 lines 41-50)

nucleotide triphophates (see col. 24 lines 41-50)

an amplification oligonucleotide which in the presence of a nucleic acid analyte and under amplification conditions is extended to form part of a nucleic acid extension product containing the

target nucleic acid sequence or directs the synthesis of a nucleic acid transcription product containing the target nucleic acid sequence [see col. 24 lines 41-50, where the amplification oligonucleotide (ie primer) is extended in the presence of a nucleic acid analyte to form part of a nucleic acid extension product containing the target nucleic acid sequence, as is necessarily the case with PCR amplification of a target nucleic acid]

With regard to claims 522 and 542, Tyagi et al. teach the first base region contains at least one ribonucleotide wherein the first base region complexes with the target nucleic acid sequence under the nucleic acid assay conditions (see Figures 1 and 2, where both the first base region and the second base region complex with the target nucleic acid. With respect to the ribonucleotide, Tyagi does not exemplify a probe with a ribonucleotide, however Tyagi teaches the probes comprise RNA and mixtures of RNA and DNA see claim 20. A probe comprising RNA necessarily has a ribonucleotide in the first base region of the probe. Additionally, a skilled artisan would be motivated to vary the ribonucleotide modifications in the probe in order to optimize probe stability and binding specificity. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regard to claims 523 and 543, Tyagi et al. teach wherein that portion of the first base region which hybridizes to the second base region includes a cluster of at least about 4 ribonucleotide (see where Tyagi teaches a ribonucleotide is present in the hairpin probe and one meets the limitation of "at least about 4")

With regard to claims 524 and 544, Tyagi et al. teach the first base region complexes with the target nucleic acid under assay conditions (see Figures 1 and 2, where both the first base region and the second base region complex with the target nucleic acid).

With regard to claims 525 and 545, Tyagi et al. teach the portion of the first base region which hybridizes to the second base region includes at least one ribonucleotide which is not a ribonucleotide modified to include a 2'-O-alkyl substitution to the ribofuranosyl moiety (see Figures 1 and 2, where the first base region and the second base region complex with one another. With respect to the ribonucleotide composition, Tyagi teaches at claim 20 the probe comprises RNA, therefore each nucleotide of the first base region is a ribonucleotide and Tyagi does not specifically teach 2'-O-alkyl substitution).

With regard to claims 526 and 546, Tyagi et al. teach the first base region complexes with the target nucleic acid sequence under the nucleic acid assay conditions (see Figures 1 and 2, where both the first base region and the second base region complex with the target nucleic acid).

With regard to claims 527 and 547, Tyagi et al. teach each nucleotide of that portion of the first base region which hybridizes to the second base region is a ribonucleotide (see Figures 1 and 2, where the first base region and the second base region complex with one another. With respect to the ribonucleotide composition, Tyagi teaches at claim 20 the probe comprises RNA, therefore each nucleotide of the first base region is a ribonucleotide).

With regard to claims 528 and 548, Tyagi et al. teach the first base region complexes with the target nucleic acid sequence under nucleic acid conditions (see Figures 1 and 2, where both the first base region and the second base region complex with the target nucleic acid).

With regard to claims 530 and 550, Tyagi et al. teach the first and second base regions form a hybrid that is more stable than a hybrid formed between unmodified forms of the first and second base regions (see claim 20, where Tyagi teaches probes with a mix of RNA and DNA. Stabilization of a hybrid having a modification is a characteristic that all probes having a mix of DNA and RNA will have. Tyagi teaches probes having a mix of DNA and RNA, therefore the probes of Tyagi will also possess a greater degree of hybrid stabilization than unmodified probes).

With regard to claims 531 and 551, Tyagi et al. teach the probe includes a conjugate molecule (see Figures 1, 2 and 3, where the conjugate is the label)

With regard to claims 532 and 552, Tyagi et al. teach the probe includes a conjugate molecule joined to the probe at a site located within the cluster of the first base region (see Figures 1, 2 and 3)

With regard to claims 533 and 553, Tyagi et al. teach the first and second base regions are contained within an oligonucleotide that is between 10 and 100 bases in length (see Figure 3)

With regard to claims 534 and 554, Tyagi et al. teach the probe comprises a detectable label (see Figure 3)

With regard to claims 535 and 555, Tyagi et al. teach the detectable label comprises a fluorescent molecule (see col. 17, where EDANS and DABCYL are recited)

With regard to claims 536 and 556, Tyagi et al. teach the nucleic acid analyte comprises RNA (see example VII, where the target is ribosomal RNA).

With regard to claims 537 and 557, Tyagi et al. teach the RNA is ribosomal RNA (see example VII, where the target is ribosomal RNA).

With regard to claims 538 and 558, Tyagi et al. teach a target sequence contained within the target nucleic acid includes a double stranded region (see Figure 2).

With regard to claim 540, Tyagi et al. teach a reaction mixture comprising

One or more amplification oligonucleotides in the presence of at lest one nucleic acid polymerase and nucleotide triphophates sufficient to form a nucleic acid amplification product, and a probe molecule comprising complementary first and second base regions that form a hybrid containing at least one ribonucleotide wherein the probe forms a stable complex with the target nucleic acid sequence but not with a non-targeted nucleic acid under nucleic acid assay conditions such that the target nucleic acid sequence can be detected and wherein the complex comprises a single stranded form of the probe (see col. 24 lines 41-50 and see col. 24 lines 41-50, where the amplification oligonucleotide (ie primer) is extended

in the presence of a nucleic acid analyte to form part of a nucleic acid extension product containing the target nucleic acid sequence, as is necessarily the case with PCR amplification of a target nucleic acid. With respect to the probe see Figures 3 and 9. With respect to the "at least one ribonucleotide see claim 20 and col. 8 lines 66-67.)

With regard to claim 541, Tyagi et al. teach one or more amplification oligonucleotides and the probe are present in the reaction mixture when the amplification reaction is initiated (see col. 24 lines 41-50, where the amplification oligonucleotide (ie primer) is extended in the presence of a nucleic acid analyte to form part of a nucleic acid extension product containing the target nucleic acid sequence, as is necessarily the case with PCR amplification of a target nucleic acid).

Tyagi et al. do not teach all of the limitations of claims 519-559, specifically, Tyagi does not teach 2'-O-alkyl-substitution of the probe.

McGall et al. teach oligonucleotide analogue arrays, specifically probes with 2'-O-alkyl substitution (see col. 2 lines 62-67 and col. 3 lines 1-2).

With regard 529, McGall et al. teach each nucleotide of the probe is a ribonucleotide (see col. 17 example 2 and Table 2).

With regard to claims 539 and 559, McGall et al. teach the 2'-O-alkyl substitution to the ribofuranosyl moiety is a 2'-O-methyl substitution (see col. 2 lines 62-67 and col. 3 lines 1-2).

With regard to claim 549, McGAll et al. teach 2'-O-methyl substitution (see col. 2 lines 62-67 and col. 3 lines 1-2) With respect to each nucleotide of the probe having this substitution, McGall does not exemplify a probe, where each nucleotide contains a 2'-O-methyl substitution, however McGall teaches the probes comprise 2'-O-methyl substitution (see col. 2 lines 62-67 and col. 3 lines 1-2). Additionally, a skilled artisan would be motivated to modify each nucleotide in the probe in order to optimize probe stability and binding specificity. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence

indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regard to claims 523 and 543, Tyagi et al. teach wherein that portion of the first base region which hybridizes to the second base region includes a cluster of at least about 4 ribonucleotide (see where Tyagi teaches a ribonucleotide is present in the hairpin probe and one meets the limitation of "at least about 4")

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the 2'O-methyl substitution as taught by McGall with the hairpin beacons, as taught by Tyagi since McGall teaches that 2'O-methyl modification results in oligonucleotide probes which have higher binding affinities for complementary sequences than their unmodified counterparts. Additionally, McGall teaches that modification also results in greater stability and reduced non-specific degradation (see col. 2 lines 62-67 and col. 3 lines 1-2). Tyagi also recognizes the importance of preventing non-specific degradation and teaches modifying internulceotide linkages as a way to confer resistance to non-specific degradation and nucleases (see col. 3 lines 1-20). An ordinary practitioner would have been motivated to use the 2'O-methyl substitution as taught by McGall with the hairpin beacons, as taught by Tyagi in order to have probes which are resistant to nuclease and non-specific degradation with the additional advantage of having higher binding affinities for complementary sequences than their unmodified counterparts.

***Response to Arguments***

4. Applicants' arguments with respect to claims 450-518 have been considered but are moot in view of the cancellation of claims 450-518 and the submission of new claims 519-559. Applicants' arguments as they may relate to new claims 519-559 drawn to rejections made over Carmo-Fonseca as evidenced by Iribarren in view of Tsang are not relevant due to the new ground(s) of rejection.

*Summary*

6. No claims allowed.

*Conclusion*

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

*Correspondence*

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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hgc

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PRIMARY EXAMINER

Teresa Strzelecka
8/2/07